Hvordan kan genetiske test give et bedre bud på en prostatakræft screening?

// How can genetic tests provide a better estimate for prostate cancer screening?

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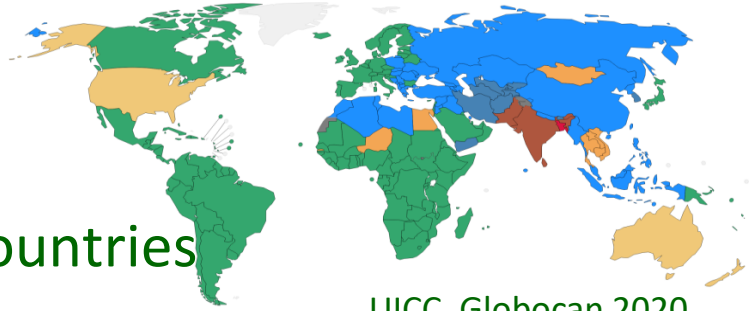
Dept Molecular Oncology, Inst Cancer Research
Oslo University Hospital – *Radiumhospitalet*

Danske Kræftforskningsdage – 31.AUG.2023

Prostate cancer



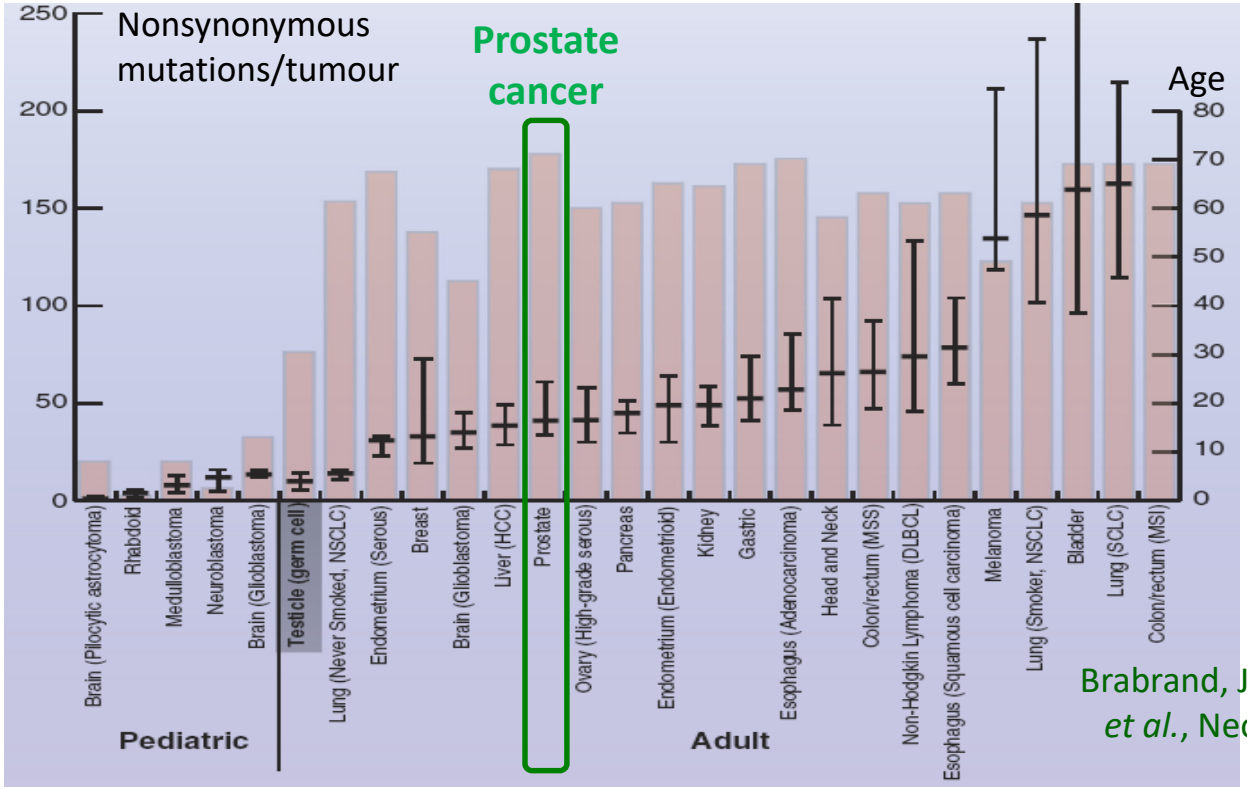
UICC, Globocan 2020

The most common male cancer in many countries

Localised prostate cancer risk stratification

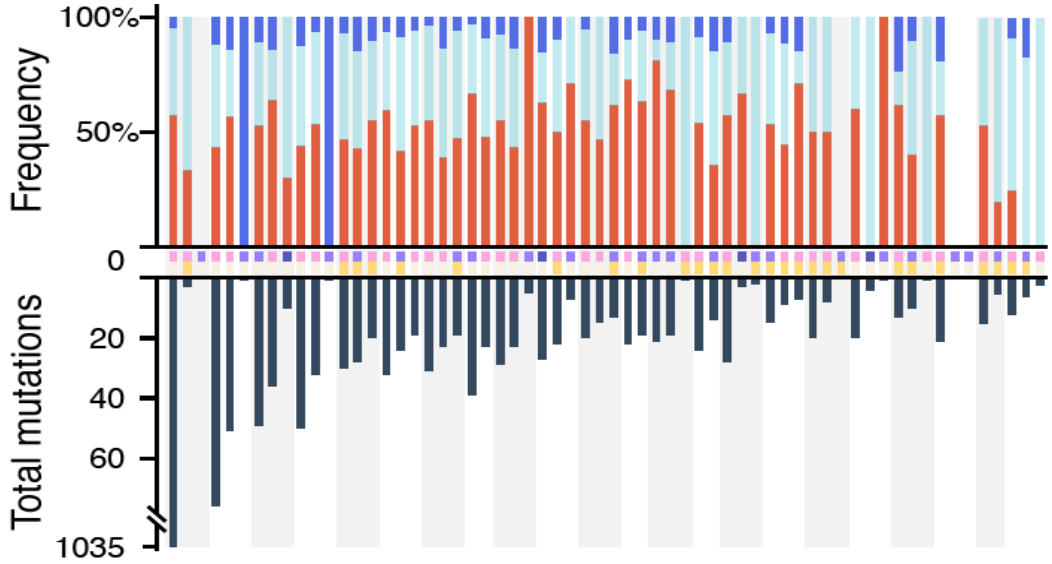
- Clinical stage, Gleason score, PSA
- Challenging to distinguish aggressive and indolent cancers
- Need for improved prognostication
- Majority have multiple primary tumour foci

Prostate cancer has relatively few somatic point mutations



Brabrand, Johannessen *et al.*, Neoplasia 2015

.. and even fewer expressed point mutations



Mutated gene not expressed
Mutated allele not expressed
Mutated allele expressed

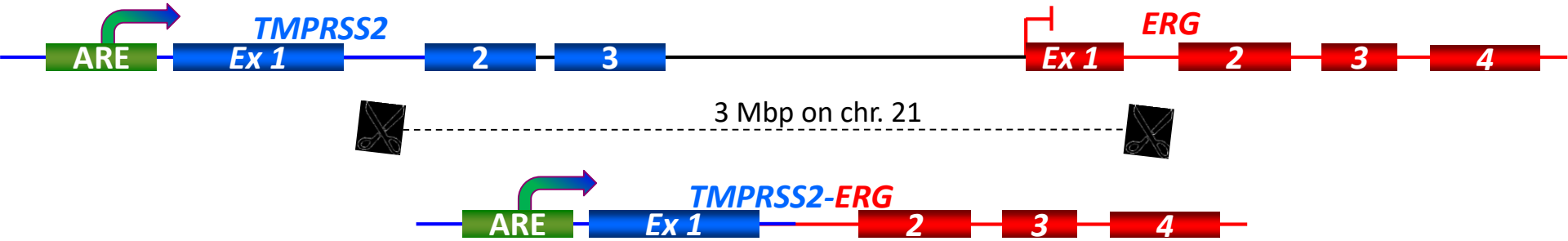
Focus 1
Focus 2
Focus 3

TMPRSS2-ERG not expressed
TMPRSS2-ERG expressed

Strømme, Johannessen *et al.*,
Cancer Gene Therapy 2022

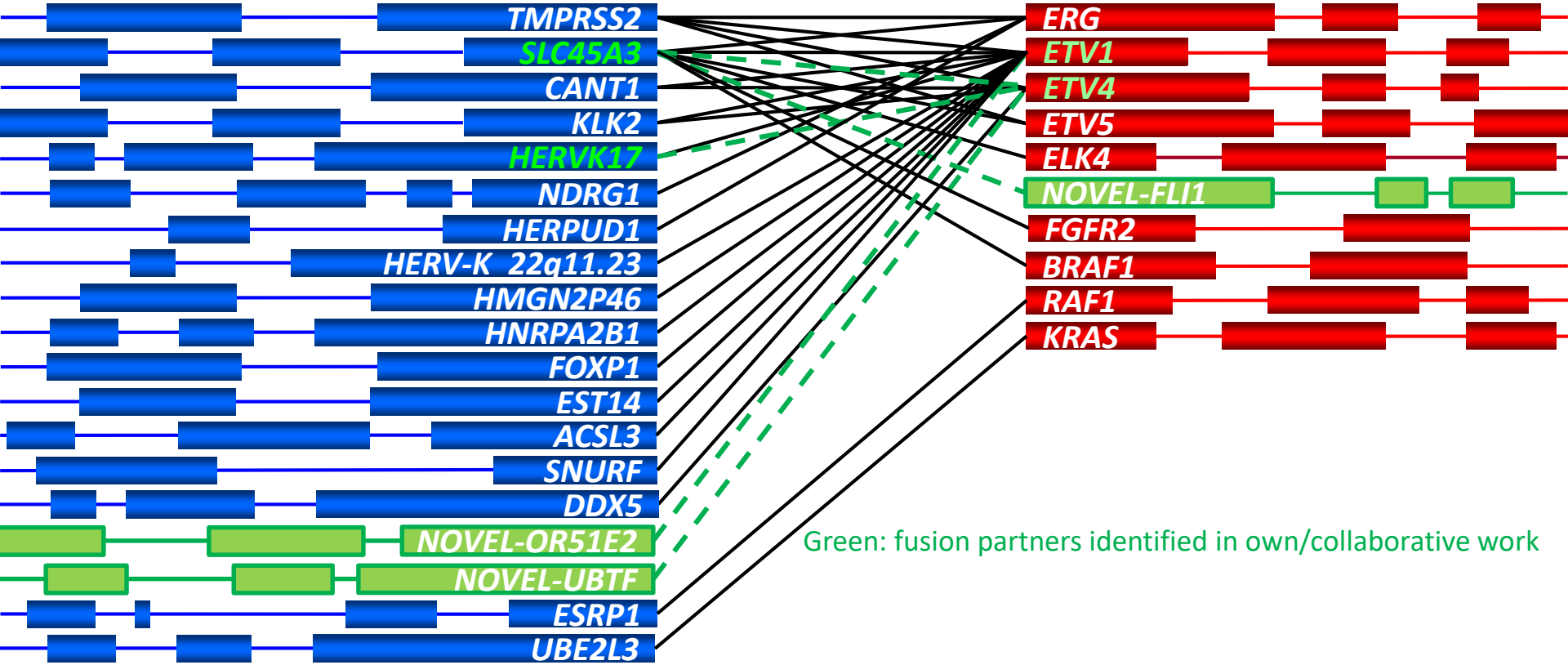
But high prevalence of the fusion *TMPRSS2-ERG*

- *ERG* encodes a transcription factor that is absent in normal prostate epithelium
- Overexpressed in about 50% of all prostate cancers, primarily through fusion with the highly expressed and androgen-regulated *TMPRSS2* gene
- The two genes are commonly fused after deletion of the 3 Mbp region that separates them on chromosome 21



Tomlins *et al.*, Science 2005

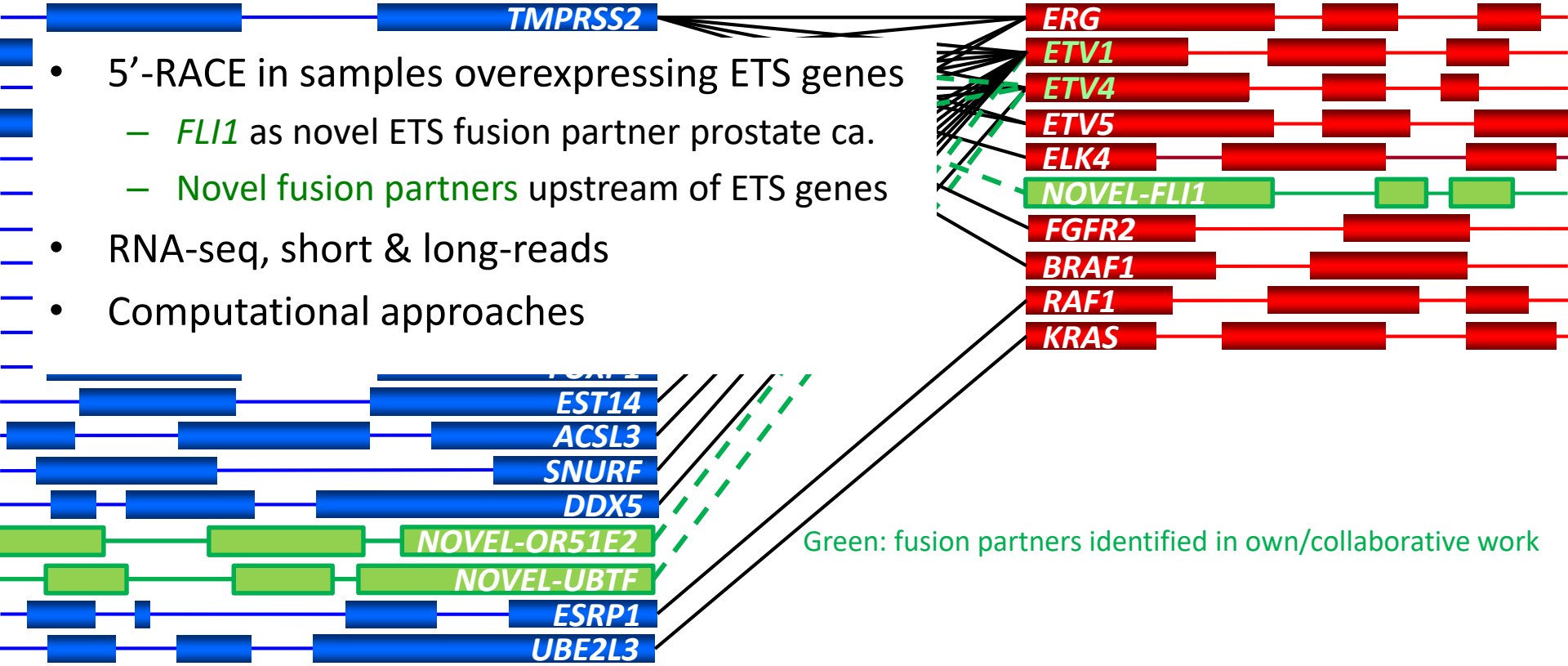
Fusion genes are common in prostate cancer



Green: fusion partners identified in own/collaborative work

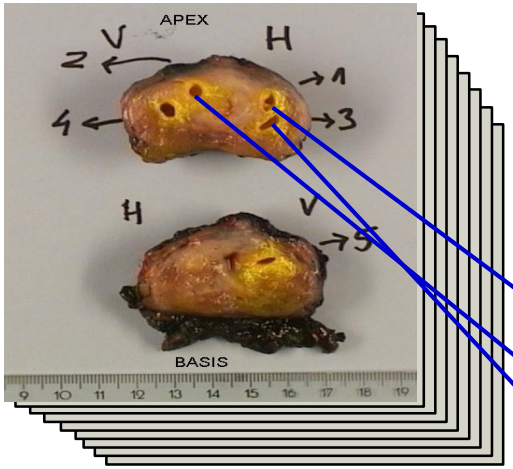
Fusion genes are common in prostate cancer

- 5’-RACE in samples overexpressing ETS genes
  - *FLI1* as novel ETS fusion partner prostate ca.
  - Novel fusion partners upstream of ETS genes
- RNA-seq, short & long-reads
- Computational approaches



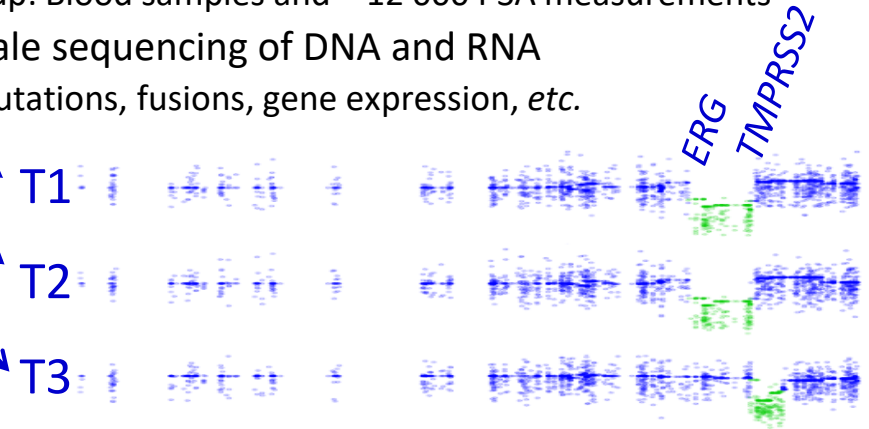
Green: fusion partners identified in own/collaborative work

Prostate cancer is commonly multifocal



Diagnostic and prognostic biomarkers may be affected by the multifocal nature of prostate cancer

- Multisampling biobank enabling hetereogeneity aware analyses
  - 3 to 7 frozen tissue samples from each of 571 patients
- Histopathological & clinical data
  - Follow-up: Blood samples and ~ 12 000 PSA measurements
- Genome-scale sequencing of DNA and RNA
  - Point mutations, fusions, gene expression, *etc.*

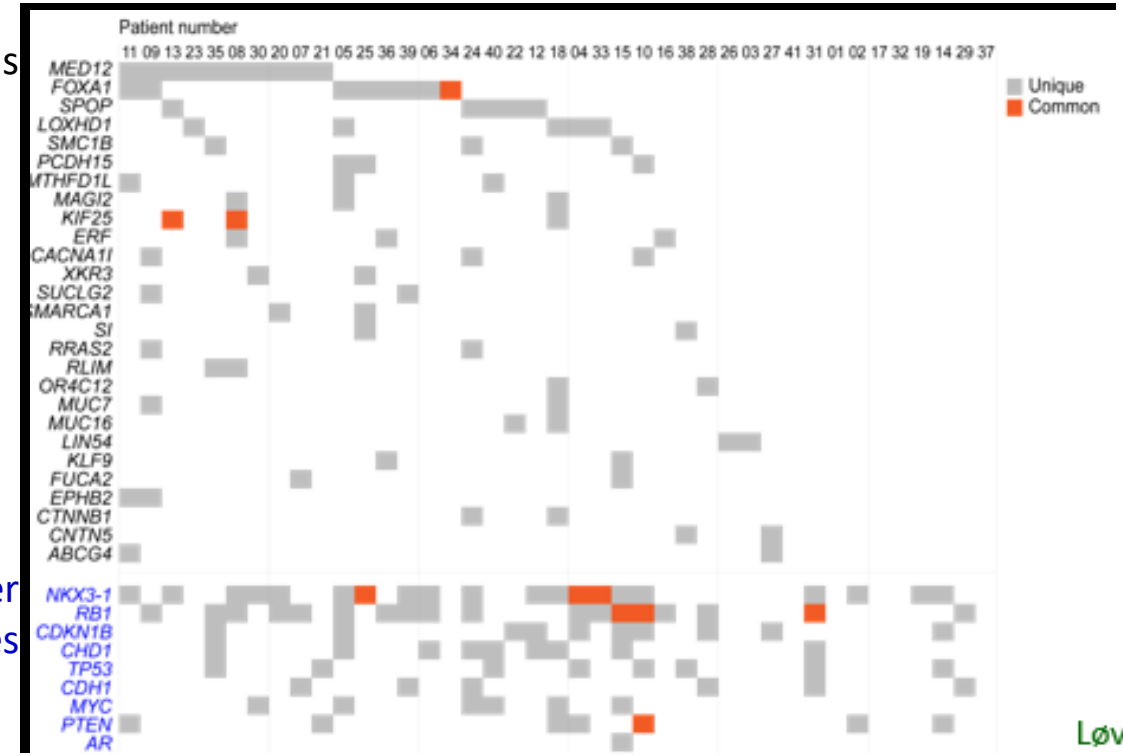


DNA copy numbers along chromosome 21 in three tumour samples from the same prostate

Point mutations and DNA copy number changes

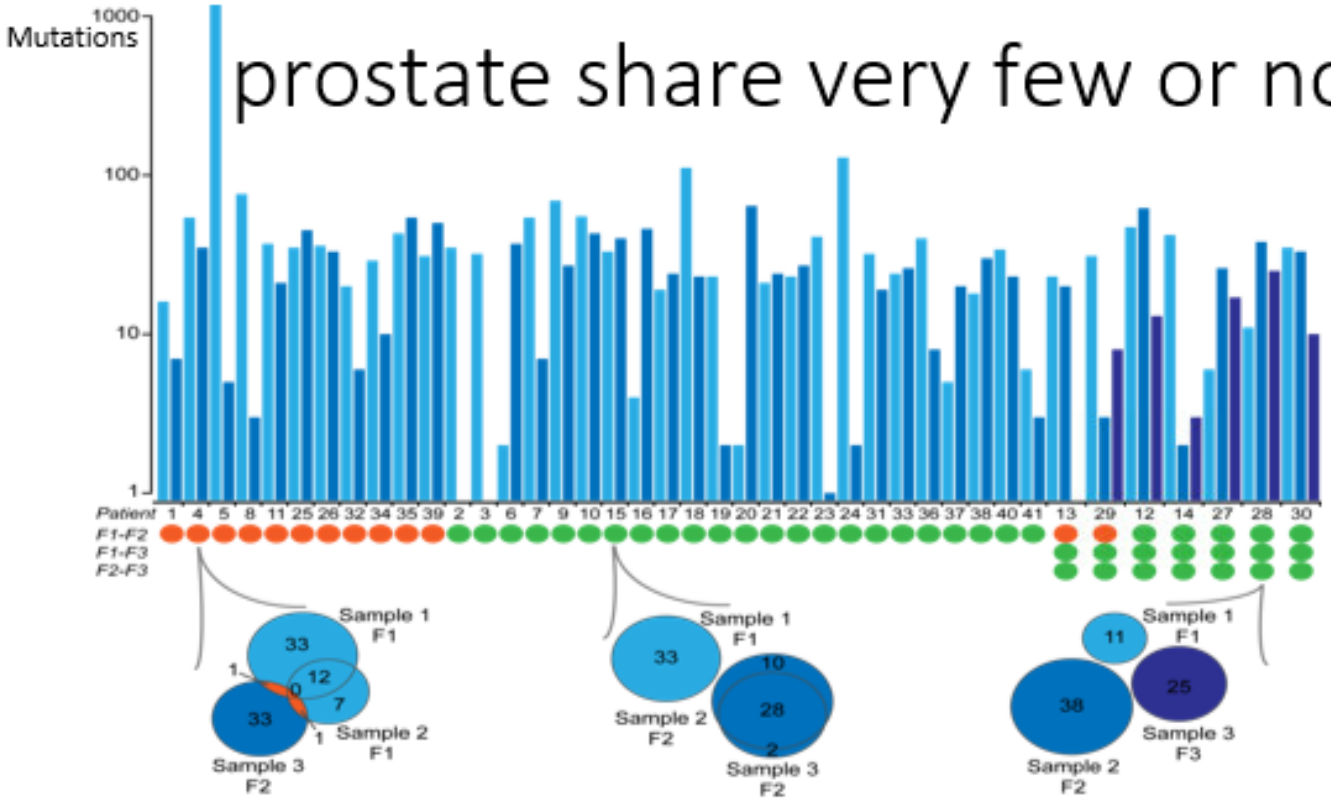
Point mutations

DNA copy number changes



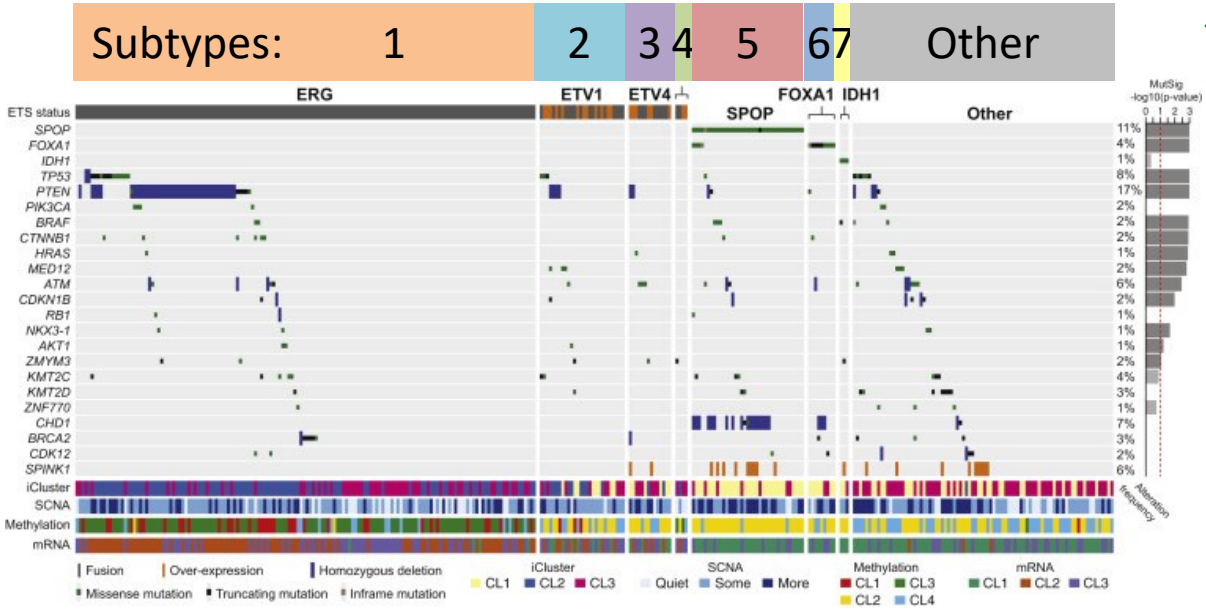
Løvf *et al.*, Eur Urol 2019

Different tumour foci from the same prostate share very few or no mutations



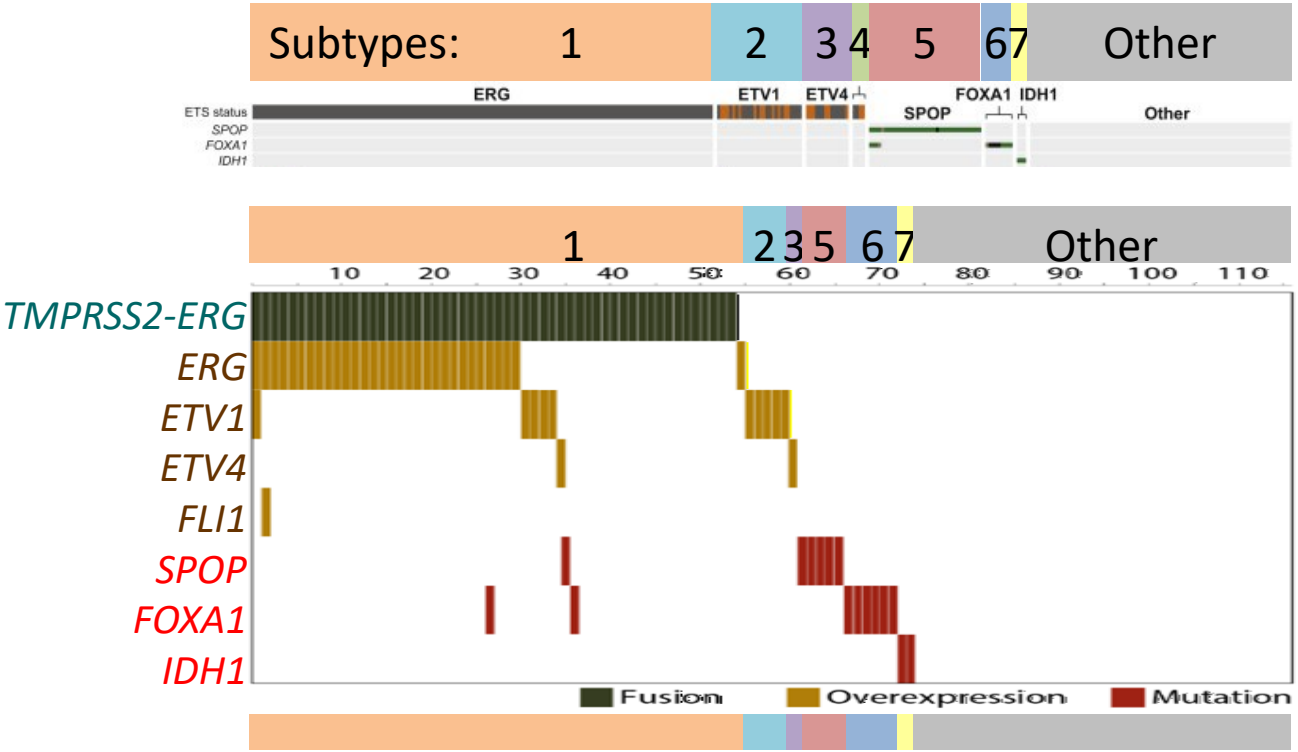
Løvf *et al.*, Eur Urol 2019

Different molecular subtypes of prostate cancer?



The Cancer Genome Atlas, Cell 2015

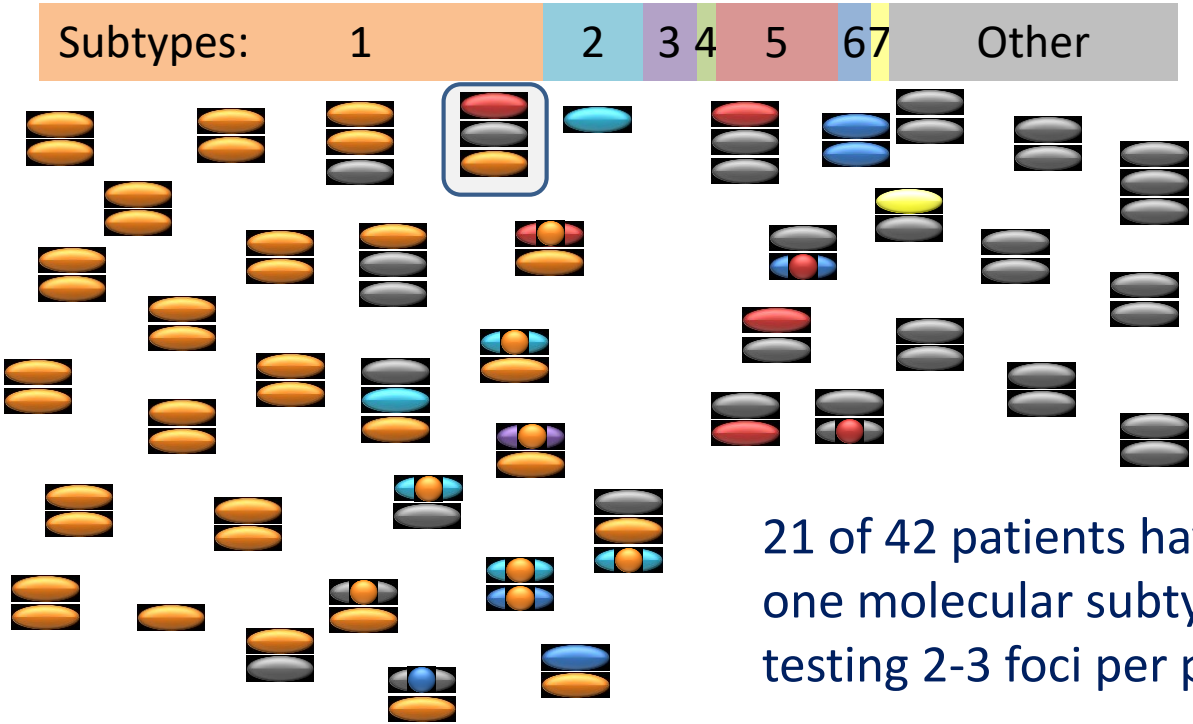
Different molecular subtypes of prostate cancer?



The Cancer Genome Atlas, Cell 2015

Cancer samples from Norwegian patients
Carm *et al.*, Sci Rep 2019

Molecular classification – per focus



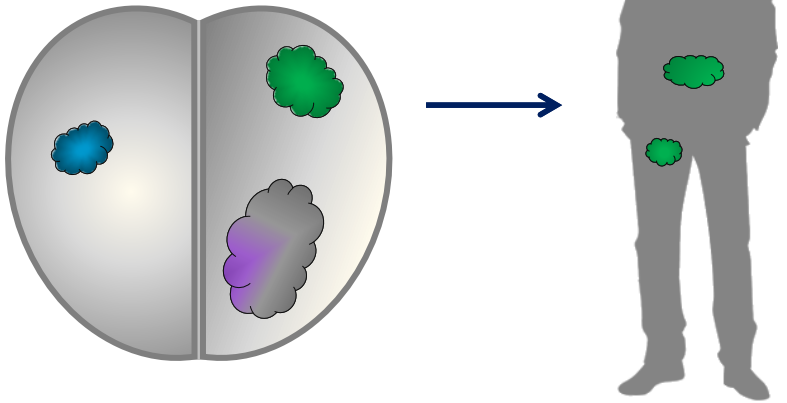
21 of 42 patients have more than one molecular subtype, when testing 2-3 foci per patient

Carm *et al.*, Sci Rep 2019

Heterogeneity in prostate cancer

- Tumour foci in primary cancers are *hetero*geneous
- Metastatic foci are to a large degree *homo*geneous

Molecular biomarkers from a random tissue sample can be irrelevant for the most significant cancer focus



Løvf *et al.*, Eur Urol 2019
Carm *et al.*, Sci Rep 2019

Liu *et al.*, Nat Med 2009
Kumar *et al.*, Nat Med 2016

Precission!

NEOPLASIA
www.neoplasia.com
Volume 23 Number xxx Month 2021 pp. 634–641

High expression of *SCHLAP1* in primary prostate cancer is an independent predictor of biochemical recurrence, despite substantial heterogeneity ☆, ☆☆

Susanne G. Kidd [a,b,#], Kristina T. Carm [a,b,#], Mari Bogaard [a,b,c], Linn Guro Olsen [a], Marthe Løvf [a], Anne Cathrine Bakken [a], Karol Axcrona [a,d], Ragnhild A. Lothe [a,b], Ulrika Axcrona [a,d], Rolf I. Skotheim [a,b,e]

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Abstract

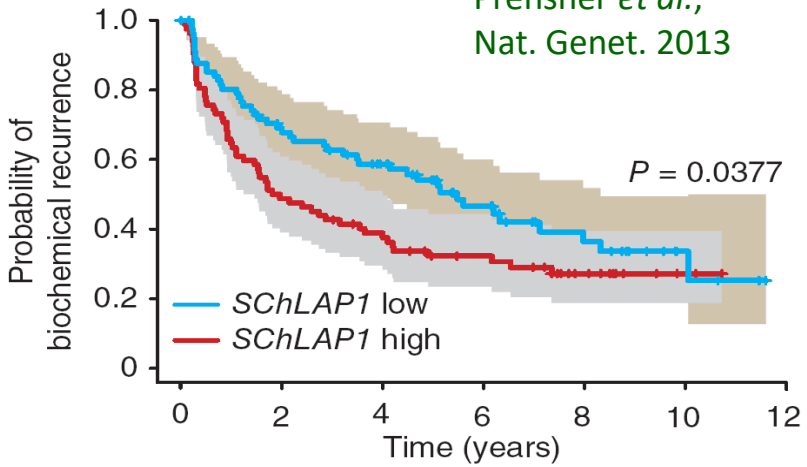
In primary prostate cancer, the common multifocality and heterogeneity are major obstacles in finding robust prognostic tissue biomarkers. The long noncoding RNA *SCHLAP1* has been suggested, but its prognostic value has not been investigated in the context of tumor heterogeneity. In the present study, expression of *SCHLAP1* was investigated using real-time RT-PCR in a multisampled series of 778 tissue samples from radical prostatectomies of 164 prostate cancer patients (median follow-up time 7.4 y). The prognostic value of *SCHLAP1* was evaluated with biochemical recurrence as endpoint.
In total, 29% of patients were classified as having high expression of *SCHLAP1* in at least one malignant sample. Among these, inter- and intrafocal heterogeneity was detected in 72% and 56%, respectively. High expression of *SCHLAP1* was shown to be a predictor of biochemical recurrence in both uni- and multivariable cox regression analyses ($P < 0.001$ and $P = 0.02$). High expression of *SCHLAP1* was also significantly associated with adverse clinicopathological characteristics, including grade, invasive cribriform growth/intraductal carcinoma of the prostate, and reactive stroma. In conclusion, high expression of *SCHLAP1* is a robust prognostic biomarker in primary prostate cancer. Importantly, although high expression of *SCHLAP1* has been associated with the aggressive histopathologic feature reactive stroma, the prognostic value of *SCHLAP1* was independent of reactive stroma. In conclusion, grade, and analysis of multiple samples is therefore crucial in determining the prognostic value of *SCHLAP1*.

Can also the management of patients with prostate cancer benefit from genomics-based precision medicine?

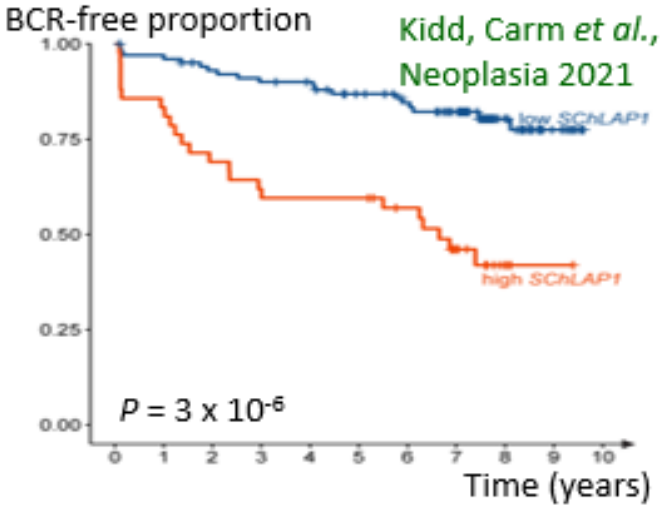
LncRNA *SChLAP1* as a tissue prognostic biomarker

- Long noncoding RNA associated with poor prognosis, particularly when heterogeneity is taken into account
- Demonstrates the potential in the biobank and our strategy for biomarker development

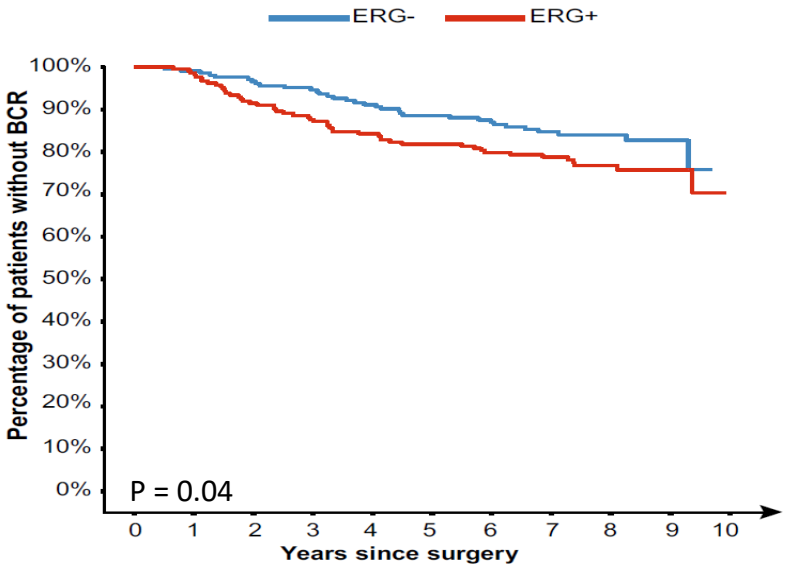
Prensner *et al.*,
Nat. Genet. 2013

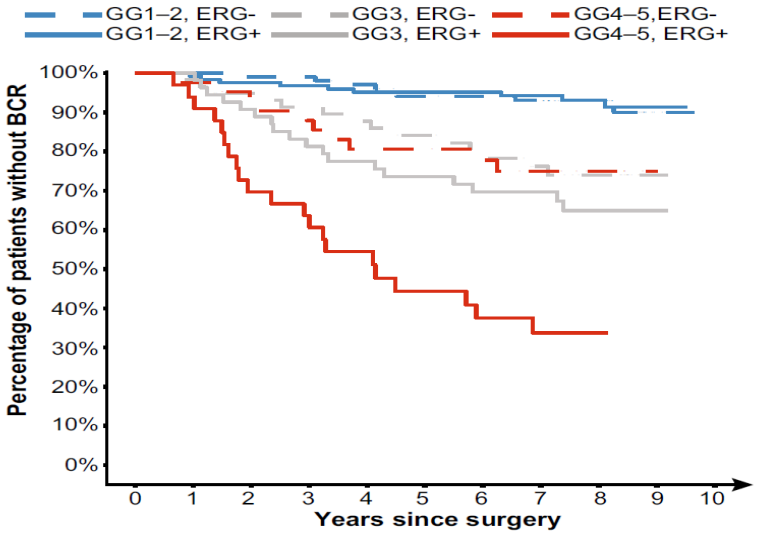


Kidd, Carm *et al.*,
Neoplasia 2021



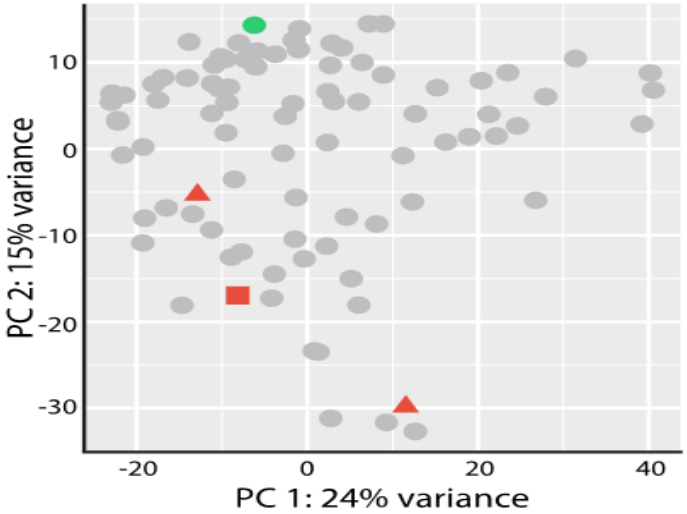
In situ expression of ERG protein in the context of tumor heterogeneity identifies prostate cancer patients with inferior prognosis





Kidd, Bogaard *et al.*, Mol Oncol 2022

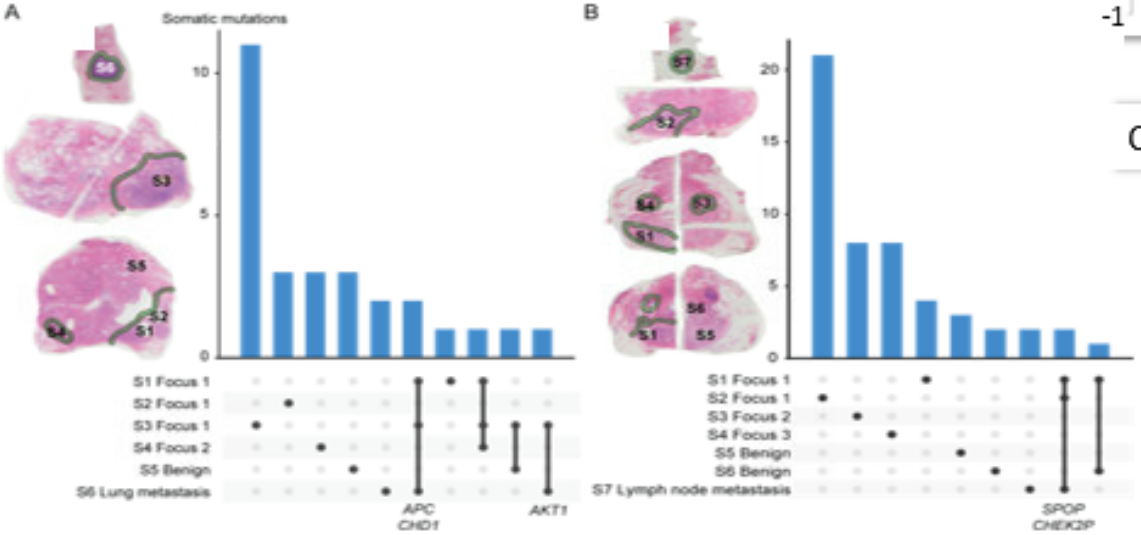
Can we identify new biomarkers, developed with heterogeneity in mind?



.. when the expression profiles from different tissue samples from the same patient are so fundamentally different?

Identification and characterisation of aggressive tumour foci

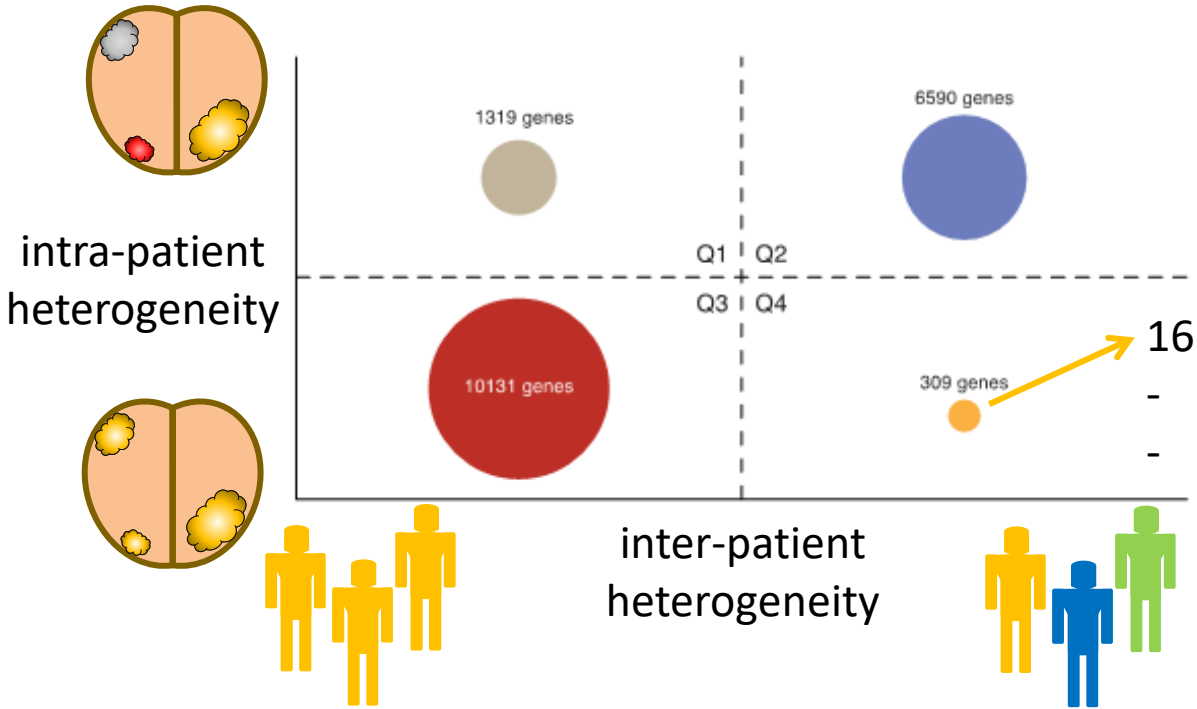
- Which tumour focus gives rise to metastasis?
- What characterizes these aggressive tumour foci (mutations, methylation, expression, ..)?



Overlapping somatic mutations

Carm *et al.*, Int J Cancer 2023

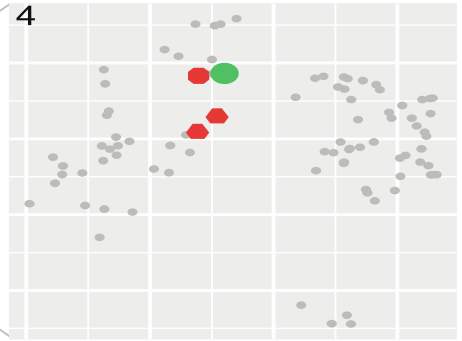
Patient specific gene expression



16 of which are
- significantly expressed
- associated with BCR

Strømme, Johannessen *et al.*, Cancer Gene Therapy 2022

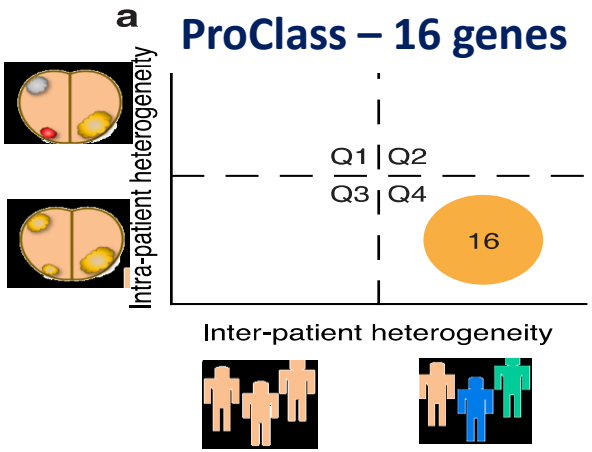
Patient specific gene expression

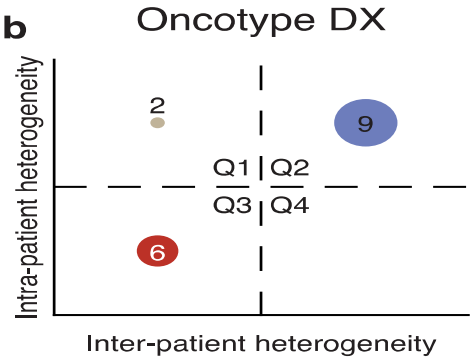


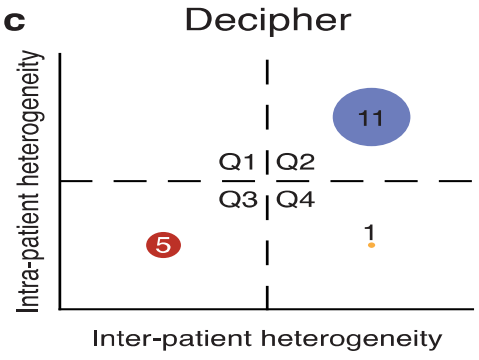
16 of which are
- significantly expressed
- associated with BCR

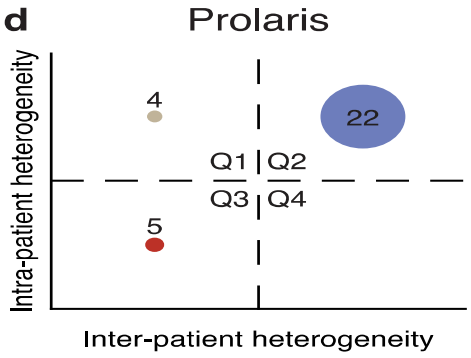
Strømme, Johannessen *et al.*,
Cancer Gene Therapy 2022

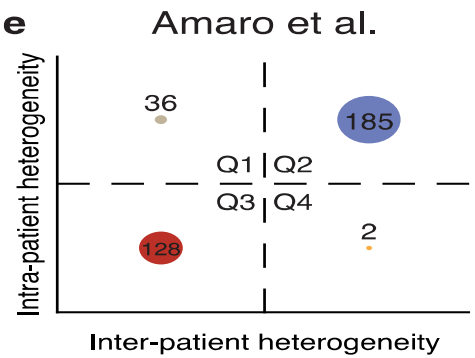
Heterogeneity quadrants for selected gene panels







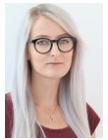




- Primary prostate cancer is commonly multifocal
- Different foci have different mutations and fusion genes
- Genomics-based precision medicine must incorporate this heterogeneity
- Either by testing all cancer foci, or through methods capturing molecular characteristics from all cancer foci, like
  - Mutations in cfDNA from plasma
  - Heterogeneity-agnostic RNA expression/DNA methylation patterns in tumour and/or benign parts of the prostate

Participants / Acknowledgements



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